REMARKS

Claim 3 has been amended as set forth above to remedy certain informalities. In particular, claim 3 has been amended to recite proper introductory Markush language (*i.e.*, "selected from the group consisting of ..."), and to add a period (.) to *S. dysenteriae* and *A. salmonicida*.

Claim 4 has been amended to recite --of the microorganism-- to make it clear what "membrane vesicle" is intended to modify. Support for this amendment is found in the specification at, for example page 10, lines 13-17.

Claim 5 has been amended to recite that the membrane vesicle "has a diameter of about 10 to about 200 nm." Support for this amendment is found in the specification at, for example page 10, lines 19-21 and lines 28-30.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments respectfully, is requested.

The Office Action, in the section entitled "Priority," asserted that "[a]n application in which the benefits of an earlier application are desired must contain a specific reference to prior application(s) in the first sentence of the specification." (Paper No. 8 at 2). In response, we note that on page 2 of the transmittal letter (copy attached as Exhibit 1) accompanying the present application contained a preliminary amendment which directed that the specification be amended by inserting before the first sentence the following:

> This application is a Continuation of application Serial No. 08/691,484 filed August 2, 1996, which claims benefit under Title 35, United States Code §119(e) of Provisional application no. 60/001,903. Filed 4 August 1995, which application(s) are incorporated by reference.

In view of this Preliminary Amendment, it is submitted that the claim for benefit has been perfected. Accordingly, it is requested that the Examiner, in the next Official Action, confirm that the claim for benefit has been perfected, and that no further action is required on the part of applicants.

We hereby affirm the election of the subject matter of Group I (claims 1-6), and the Examiner's withdrawal of the election of species requirement. (Paper No. 8 at 2).

Claim 3 was objected to because the abbreviation for *Aeromonas* did not contain a period (.). (*Id.*). With a view toward furthering prosecution, claim 3 has been amended to add a period after "*A.*" In view of this amendment, the rejection has been rendered moot. Accordingly, withdrawal of the objection, respectfully is requested.

Claims 1-6 were rejected under 35 USC §112, second paragraph for a number of reasons. (*Id.* at 3). In making the rejection of claims 1 and 6, the Examiner contended that the term "carrier strain" is unclear. (*Id.*).

For the reasons set forth below, this rejection, respectfully is traversed.

As is well settled, in rejecting a claim under the second paragraph of section 112, it is incumbent on the Examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Ex parte Wu*, 10 USPQ2d 2031, 2032-33 (BPAI 1989) (on request for reconsideration by the Examiner) (*citing In re Moore*). This, the rejection does not do. For example, the rejection does not make a single factual determination that establishes that one of ordinary skill in this art "would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims" based

upon the term "carrier strain" as used in claims 1 and 6. For this reason alone, the rejection is insufficient as a matter of law, and should be withdrawn.

Notwithstanding the legal insufficiency of the rejection, we note that the use of the phrase "carrier strain" in claims 1 and 6 is not indefinite, and the scope of the respective claims would be readily understood by one skilled in this art with reference to the claims, as well as the specification.

For example, the following recitations from the specification clearly identify the metes and bounds of the term "carrier strain" as it is used in claims 1 and 6:

> Broadly stated, the present invention relates to a vaccine against an infectious disease caused by an infectious agent comprising ***a carrier strain having a membrane vesicle of a microorganism integrated into the cell surface of the carrier strain***, wherein the membrane vesicle has an amount of an antigen associated with its cell surface which is effect to provide protection against the infectious agent.
> (Page 3, line 32 to Page 4, line 3).

> ***The carrier strain is selected so that it is incapable of multiplying in vivo***. Carrier strains are obtained through selection of variants which occur naturally, or using conventional means known to those skilled in the art. Examples of suitable carrier strains are *Shigella* species, *Salmonella* species, preferably *S. typhi* Ty21a, *S. typhimirium*, *Vibrio* species, and *Escherichia* species.
> (Page 19, lines 20-25)

In addition, Example 2 discloses an experiment showing the integration of the membrane vesicle's membrane with a carrier strain. Note in particular Figures 11A-E which show that the gold particles of an immunogold EM study specifically labeled the foreign antigens ***on a carrier strain***.

Based on these, and other disclosures in the specification, it is respectfully submitted that the term "carrier strain" is an art accepted term that is not only defined in the

specification but is described in the examples, and shown in the figures. Thus, one skilled in this art would understand what is intended by the use of the phrase "carrier strain." Nothing more is required. Accordingly, withdrawal of the rejection of claims 1 and 6, respectfully is requested.

Regarding the §112, second paragraph rejection of claim 3, the Examiner contended that it contained "improper Markush language." (Paper No. 8 at 3). With a view toward furthering prosecution, claim 3 has been amended to recite "selected from the group consisting of." In view of this amendment, the rejection is rendered moot, and should be withdrawn.

Regarding the §112, second paragraph rejection of claim 4, the Examiner contended that the recitation of the phrase "the membrane vesicle is a natural membrane vesicle of the microorganism containing outer membrane and periplasm components" is unclear. (*Id.*). With a view toward furthering prosecution, claim 4 has been amended to recite that "the membrane vesicle of the microorganism is a natural membrane vesicle of the microorganism containing outer membrane and periplasm components." Thus, it is clear that the "membrane vesicle" referred to in claim 4 is the membrane vesicle of the microorganism. In view of this amendment, the rejection is rendered moot, and should be withdrawn.

Regarding the §112, second paragraph rejection of claim 5, the Examiner contended that the recitation of the phrase "a large membrane vesicle" is vague and indefinite. (*Id.* at 4). With a view toward furthering prosecution, claim 5 has been amended to recite that the membrane vesicle has a diameter of about 10 to about 200 nm. In view of this amendment, the rejection is rendered moot, and should be withdrawn.

In sum, in view of the amendments and arguments set forth above, all of the 35 USC §112, second paragraph rejections are overcome or rendered moot. Accordingly, withdrawal of all of the §112, second paragraph rejections, respectfully is requested.

Claims 1-6 were rejected under 35 USC §103(a) as unpatentable over Hamstra *et al.* WO 92/05194 ("Hamstra") in view of Viret *et al.* EP 564 689 ("Viret") and Van Der Ley *et al.* WO 94/08021 ("Van Der Ley"). (Paper No. 8 at 5).

For the reasons set forth below, this rejection, respectfully is traversed.

Hamstra disclose a vaccine for combating *Bordetella pertussis*, which includes as an active agent one or more outer membrane proteins (OMPs) derived from *B. pertussis* or from genetically manipulated microorganisms producing the OMPs. (Abstract). Hamstra disclose that "***in light of the ... disadvantages associated with B. pertussis 'whole-cell" vaccines***, which vaccines contain a variety of substances, such as for example, proteins, nucleic acids, peptidoglucans, lipids and lipopolysaccharides, ***a broad-based study has been started to develop acellular vaccines***, with which, in the optimum case, only those antigens which generate adequate immunity and themselves display no toxicity should be allowed to be present." (Page 2, lines 2-9). The vaccines are disclosed to be "effective, non-toxic ***acellular*** *B. pertussis* vaccines." (Page 3, lines 3-4). The OMPs "preferably" are present in an outer membrane vesicle (OMV) formulation or an artificial vesicle formulation. (*Id.* at lines 9-10).

Viret disclose recombinant live attenuated bacterial strains expressing O-serotype determinants of gram-negative enteric pathogens in a form covalently bound to a lipopolysaccharide (LPS) core. (Abstract). These recombinant carrier strains are disclosed to be used as live vaccines for oral immunization. (*Id.*). The recombinant live vaccine includes a bacterial strain that has been modified via recombinant DNA technology so that it carries and

expresses at least one set of heterologous genes, wherein expression of said heterologous genes results in (a) new immunogenic property(ies) of said strain...." (page 3, lines 41-44). Viret define "carrier strain" to mean "an attenuated bacterial strain carrying and expressing one or more foreign genetic determinants encoding protective antigens from a heterologous bacterium pathogenic for humans." (Page 3, lines 46-48).

Van Der Ley disclose an immunity providing B cell activating molecule derived from a *meningococcal* lipopolysaccharide (LPS) having at least one epitope. (Abstract). The B cell activating molecule is disclosed to have at least the communal part of the oligosaccharide of the lipopolysaccharides specific for at least two *meningococcal* immunotypes. (*Id.*). Van Der Ley also disclose an outer membrane vesicle (OMV) provided with a group of polypeptides having at least the immunoactivity of outer membrane proteins (OMPs) bound to a membrane, a polypeptide from the group of the outer membrane vesicles being a membrane anchored OMP or OMP fragment with a mutation in one of the surface loops. (*Id.*).

In Van Der Ley, the OMVs were made according to the process disclosed in Fredriksen, *et al.* Production, Characterization and Control of MenB-Vaccine <<Folkehelsa>>: An Outer Membrane Vesicle Vaccine Against Group B Meningococcal Disease, *NIPH Annals*, 14(2):67-80 (1991) ("Fredriksen")(copy attached as Exhibit 2). (Van Der Ley, page 15, lines 27-31). Thus, the OMVs were produced by extracting *meningococcus* biomass with EDTA and deoxycholate (DOC). (*See* Fredriksen, page 69).

In making the rejection, the Examiner contended that Hamstra disclose vaccines against *B. pertussis* that contain one or more outer membrane proteins in an outer membrane vesicle. (Paper No. 8 at 5). The Examiner acknowledged, however, that Hamstra differ from the present claims in that they do not disclose a vaccine comprising a carrier strain having a

membrane vesicle of a microorganism integrated into its cell surface, and wherein the membrane has an antigen associated with its surface." (*Id.*). To fill this acknowledged gap, the Examiner relied on Viret as disclosing strains of attenuated live recombinant bacteria that express O-serotype determinants of gram-negative enteric pathogens which are covalently bound to a lipopolysaccharide core, and Van Der Ley as disclosing the use of outer membrane vesicles in combination with a group of polypeptides, with the immunoactivity of the outer membrane proteins, bound to a membrane. (*Id.* at 5-6).

The Examiner concluded that it would have been obvious to have incorporated the outer membrane vesicles into a vaccine formulation as disclosed by Hamstra and Van Der Ley and to further incorporate the membrane vesicle into the surface of a carrier strain as taught by Viret. (*Id.* at 6).

For the reasons set forth below, this rejection, respectfully is traversed.

As noted above, Hamstra disclose ***acellular*** vaccines. (page 2, line 6). Such ***acellular*** vaccines were developed by Hamstra to overcome the "disadvantages" associated with *B. pertussis* "whole cell" vaccines. (*Id.* at lines 2-3). Thus, the entire disclosure in Hamstra is directed away from the use of cellular vaccines. In contrast to Hamstra, claim 1 recites a vaccine comprising a carrier strain having a membrane vesicle of a microorganism integrated into the cell surface of the carrier strain. Thus, the presently claimed vaccine is clearly a ***cellular*** vaccine. Based on Hamstra as a whole then, one skilled in this art would be lead away from the present invention.

As is well settled, the Examiner has the burden of establishing (1) that there is a suggestion or motivation to combine the references relied upon, and (2) that the references, when so combined, contain the requisite suggestion and motivation that would have led one to combine

the particular disclosure relied upon and to make a composition as claimed. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

Here, the Examiner has not provided ***any*** reason ***why*** one would have selected Hamstra and Van Der Ley, which disclose ***acellular*** vaccines, and combined such acellular vaccine systems with a ***cellular*** vaccine system as disclosed in Viret to arrive at the present claims. That, however, was the Examiner's burden.

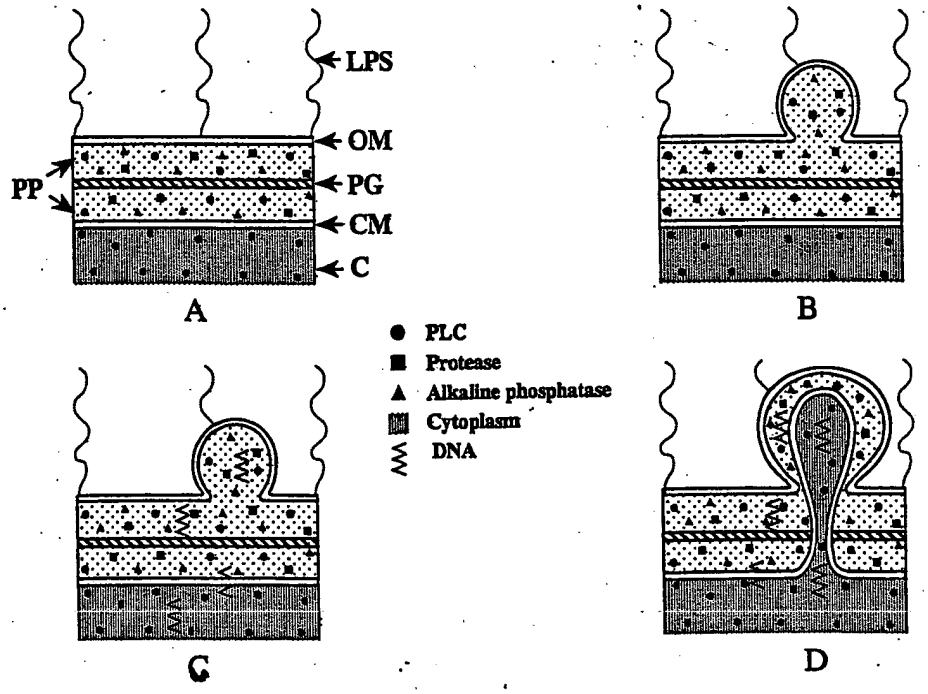
In short, the Examiner was required to demonstrate ***where*** in Hamstra, Van Der Ley, or Viret there is a suggestion which would have "strongly motivated" one to substitute an ***acellular*** vaccine for a cellular vaccine as claimed. *Ex parte Graselli*, 231 USPQ 393, 394 (Bd. App. 1986). The type of motivation which would have "***impelled***" one to do so (*Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993)), and the type of suggestion that the changes "***should***" be made. *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. App. 1964).

Because the rejection has not identified ***any*** suggestion, reason, or other motivation, including suggestion of desirability, for ***why*** one would have been led to pick the ***acellular*** vaccine system (Hamstra and Van Der Ley), and combine it with a ***cellular*** vaccine system (Viret) to arrive at a cellular vaccine as claimed, the rejection fails to set forth the required facts and reasoning required to support a *prima facie* case of obviousness. For this additional reason the rejection should be withdrawn.

Moreover, the rejection fails to address Hamstra's clear teaching away (*i.e.*, the "disadvantage" of) using cellular vaccines. There is absolutely no discussion in the Office Action explaining why one skilled in this art would have ignored the express disclosure in Hamstra that cellular vaccines are "disadvantageous," and would have combined components of acellular vaccine systems (Hamstra and Van Der Ley) with the cellular vaccine system (Viret) to

arrive at the present claims. But that too was the Examiner's burden. Absent such a motivation to ignore the express teaching away in Hamstra, and to combine the cited documents as the rejection has done, the rejection is legally insufficient to support a conclusion of obviousness.

Notwithstanding the legally insufficient nature of the rejection, we demonstrate below that it is also factually insufficient to support a conclusion of obviousness. For example, claim 1 recites a vaccine comprising a carrier strain in which a ***membrane vesicle of a microorganism*** has been integrated into the cell surface of the carrier strain. As the specification indicates, "membrane vesicles also known as blebs, are little bud-like protrusions formed in the cell wall, outer membrane, cytoplasmic, and/or plasma membrane of a microorganism." (Page 10, lines 14-17). For the Examiner's convenience, such a membrane vesicle (which is depicted in Figure 10 of the specification) is set forth below:



As can be seen in the figure above, and as the specification further indicates, "[t]he membrane vesicles are characterized by having specific antigen associated with their surfaces, and containing specific enzymes, ***which are native to the microorganism from which the membrane vesicles are derived.***" (Page 12, lines 20-23). Thus, the membrane vesicle recited by claim 1 contains ***native*** antigens and enzymes.

The rejection, however, fails to identify where in any of the cited documents membrane vesicles of ***native*** antigens and enzymes can be found, even though it recognizes that Hamstra does not disclose such a limitation. (Paper No. 11 at 5). At most, the rejection summarily concludes that such a limitation would have been obvious because (a) Van Der Ley use "membrane vesicles as vaccine components" and (b) Viret disclose that "antigens expressed on the surface of a carrier strain stimulate the immune system and elicit a protective response." (*Id.* at 6).

Such a conclusion, however, is inconsistent with a review of the secondary documents relied on in the rejection. For example, Viret uses complicated recombinant techniques to introduce antigenic components, *i.e.*, O-serotype determinants of gram-negative enteric pathogens onto the surface of its carrier strain. Thus, Viret discloses, that "upon cloning and transfer of a compatible set of genes into a suitable vaccine strain, said strain will express a complete LPS structure with the O-antigen of the pathogen displayed on its surface. As a result of this surface expression, the immune system of the vaccines is stimulated and a protective immune response, *e.g.* against *S. sonnei*, induced." (Page 4, lines 26-29). Accordingly, in Viret, immunity is accomplished by expressing recombinant proteins on the cell surface of the carrier strain - not by a "true" membrane vesicle as presently claimed. And, the rejection points to no

disclosure in Viret of a ***membrane vesicle from a microorganism*** having an antigen associated with its cell surface as recited in claim 1.

Similarly, the rejection points to no disclosure in Van Der Ley of a "membrane vesicle from a microorganism" as recited in claim 1. Rather, as noted above, in the Van Der Ley process, outer membrane proteins are ***extracted*** from *meningococci* using the Fredriksen method. (Van Der Ley, page 15, lines 27-31). In this method, the *meningococci* are treated with EDTA and deoxycholate, which results in "membrane pieces," and not "membrane vesicles" as recited in claim 1. Moreover, such "membrane pieces" are modified chemically to make them more suitable for coupling with an immunoactive component. (Van Der Ley, page 16, line 11- Page 17, line 12.

Thus, even if Viret and Van Der Ley are properly combinable with Hamstra, which is not admitted, they fail to remedy the acknowledged gap, *i.e.*, they do not disclose a "membrane vesicle from a microorganism." For this reason also, the rejection should be withdrawn.

In sum, the rejection is legally and factually insufficient to support a conclusion of obviousness. Accordingly, withdrawal of the rejection of claims 1-6, respectfully is requested.

For the reasons set forth above, favorable action on the merits, including entry of the amendments, withdrawal of the objection and rejections, and allowance of the claims is respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231, on January 3, 2001.

Kevin C. Hooper

Respectfully submitted,

By: _____

Kevin C. Hooper
Registration No. 40,402
BRYAN CAVE LLP
245 Park Avenue
New York, NY 10167-0034
(212) 692-1800